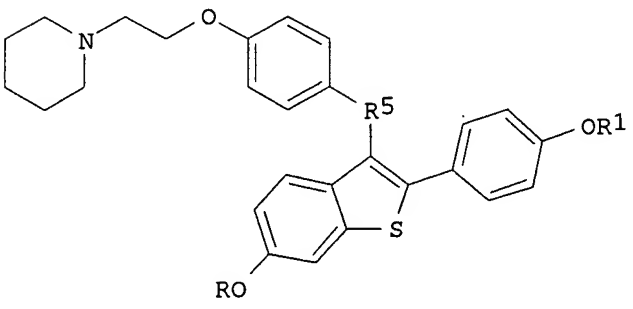
L3 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:550743 HCAPLUS
DOCUMENT NUMBER: 141:82310
ENTRY DATE: Entered STN: 09 Jul 2004
TITLE: Use of benzothiophenes and optional estrogen-lowering agents to treat and prevent prostate cancer
INVENTOR(S): Agus, David B.
PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, USA
SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Pat. Appl. 2002 198,235.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K031-453
US PATENT CLASSIF.: 514320000
CLASSIFICATION: 1-6 (Pharmacology)
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
US 2004132776	A1	20040708	US 2003-625152		20030723	<--
US 2002198235	A1	20021226	US 2002-142087		20020509	
PRIORITY APPLN. INFO.:			US 2002-142087	A2	20020509	
			US 2001-290307P	P	20010510	

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
US 2004132776	ICM	A61K031-453	
	INCL	514320000	
US 2004132776	NCL	514/320.000	
	ECLA	A61K031/4535	<--
US 2002198235	NCL	514/320.000	
	ECLA	A61K031/4535	

OTHER SOURCE(S): MARPAT 141:82310
GRAPHIC IMAGE:



I

ABSTRACT:
A method is disclosed for treating and preventing prostate cancer, particularly androgen-independent prostate cancer, the method including administering to a mammal a benzothiopene I (R, R1 = H, COR2, COR3, R4; R2 = H, C1-14 alkyl, C1-3

chloroalkyl, C1-3 fluoroalkyl, C5-7 cycloalkyl, C1-4 alkoxy, Ph; R3 = substituted Ph; R4 = C1-4 alkyl, C5-7 cycloalkyl, benzyl; R5 = O, C=O), or pharmaceutically acceptable salts or prodrugs thereof. The method may further include the administration of an estrogen-lowering drug to enhance efficacy of the compound of the invention.

SUPPL. TERM: benzothiophene deriv prostate cancer antitumor; estrogen lowering agent benzothiophene deriv prostate cancer antitumor

INDEX TERM: Androgens
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(androgen-independent prostate cancer; benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

INDEX TERM: Antitumor agents
Drug toxicity
Human
Prostate gland, neoplasm
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

INDEX TERM: Prostate-specific antigen
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

INDEX TERM: Estrogens
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(estrogen-lowering drugs; benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

INDEX TERM: Drug delivery systems
(oral; benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

INDEX TERM: Drug delivery systems
(prodrugs; benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

INDEX TERM: **84449-90-1**
ROLE: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

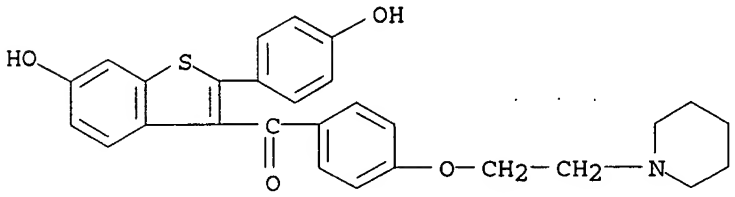
INDEX TERM: **50-28-2**, Estradiol, biological studies
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

INDEX TERM: **82640-04-8**, Raloxifene hydrochloride
176672-18-7
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

INDEX TERM: **716847-66-4 716847-67-5**
716847-68-6 716847-69-7
716847-70-0 716847-71-1

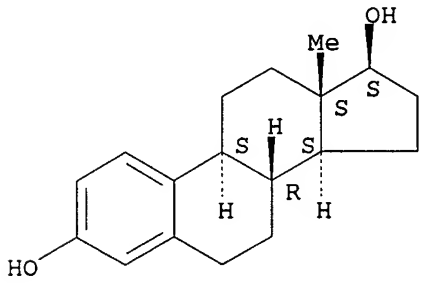
716847-72-2 716847-73-3
716847-74-4 716847-75-5
716847-76-6 716847-77-7
ROLE: PRP (Properties)
(unclaimed nucleotide sequence; use of benzothiophenes and optional estrogen-lowering agents to treat and prevent prostate cancer)

IT **84449-90-1**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)
RN 84449-90-1 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)

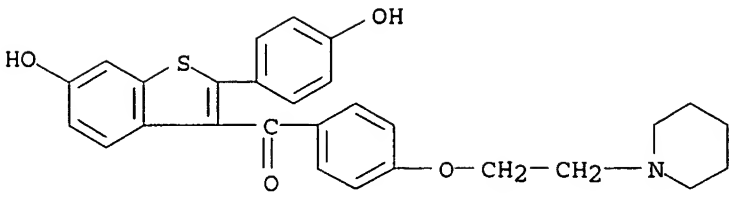


IT **50-28-2**, Estradiol, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)
RN 50-28-2 HCAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol (17β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

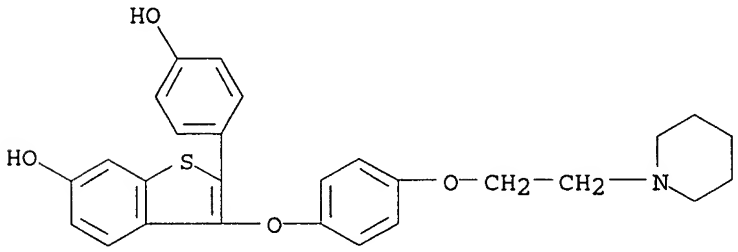


IT **82640-04-8**, Raloxifene hydrochloride **176672-18-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)
RN 82640-04-8 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 176672-18-7 HCAPLUS
CN Benzo[b]thiophene-6-ol, 2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]- (9CI) (CA INDEX NAME)



IT **716847-66-4 716847-67-5 716847-68-6**
716847-69-7 716847-70-0 716847-71-1
716847-72-2 716847-73-3 716847-74-4
716847-75-5 716847-76-6 716847-77-7
RL: PRP (Properties)
(unclaimed nucleotide sequence; use of benzothiophenes and optional estrogen-lowering agents to treat and prevent prostate cancer)
RN 716847-66-4 HCAPLUS
CN 6: PN: US20040132776 SEQID: 6 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 716847-67-5 HCAPLUS
CN 7: PN: US20040132776 SEQID: 7 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 716847-68-6 HCAPLUS
CN 8: PN: US20040132776 SEQID: 8 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 716847-69-7 HCAPLUS
CN 9: PN: US20040132776 SEQID: 9 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 716847-70-0 HCAPLUS
CN 10: PN: US20040132776 SEQID: 10 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 716847-71-1 HCAPLUS
CN 11: PN: US20040132776 SEQID: 11 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 716847-72-2 HCAPLUS
CN 12: PN: US20040132776 SEQID: 12 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 716847-73-3 HCAPLUS
CN 1: PN: US20040132776 SEQID: 1 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 716847-74-4 HCAPLUS
CN 2: PN: US20040132776 SEQID: 2 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 716847-75-5 HCAPLUS
CN 3: PN: US20040132776 SEQID: 3 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 716847-76-6 HCAPLUS
CN 4: PN: US20040132776 SEQID: 4 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 716847-77-7 HCAPLUS
CN 5: PN: US20040132776 SEQID: 5 unclaimed DNA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

(1a)

(6) Treatment Androgen Indep. PC.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L5           444 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "PROSTATE GLAND, NEOPLASM"+PFT
                 ,NT/CT(L)INDEPENDENT
L7           372 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 AND L5
L9            32 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 AND REVIEW/DT


=> d 19 ibib abs hitind 1-32

L9   ANSWER 1 OF 32  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        2005:125971  HCAPLUS
TITLE:                   Neuroendocrine cells in prostate cancer
AUTHOR(S):               Amorino, George P.; Parsons, Sarah J.
CORPORATE SOURCE:        Department of Microbiology, University of Virginia
                         Health Sciences Center, Charlottesville, VA, 22908,
                         USA
SOURCE:                  Critical Reviews in Eukaryotic Gene Expression (2004),
                         14(4), 287-300
                         CODEN: CRGEEJ; ISSN: 1045-4403
PUBLISHER:               Begell House, Inc.
DOCUMENT TYPE:           Journal; General Review
LANGUAGE:                English
AB   Neuroendocrine (NE) cells are found in prostate tumors, and their
     incidence is considered a promising prognostic indicator for the
     development of androgen-independent disease.  NE cells are derived from
     non-NE prostate cancer cells and secrete factors that can act in a
     paracrine manner to stimulate the survival, growth, motility, and
     metastatic potential of prostatic carcinoma cells.  Factors such as IL-6,
     epinephrine, and forskolin induce NE differentiation in prostate cancer
     cells; the mechanisms involve increases in intracellular cAMP, protein
     kinase A (PKA) activation and reduced intracellular calcium levels.
     Transcription factors implicated in the acquisition of NE characteristics
     by prostate cancer cells include STAT3, CREB, EGR1, c-fos, and
     NF-κB.  Expression of Chromogranin A, neuron-specific enolase,
     bcl-2, and the androgen receptor are modulated during NE differentiation
     and serve as mol. markers for NE cells.  Most importantly, NE cells
     secrete neuropeptides, such as bombesin, neurotensin, PTHrP, serotonin,
     and calcitonin, which trigger growth and survival responses in
     androgen-independent prostate cancer cells.  Prostate cancer cell
     receptors that play a role in these processes include the
     gastrin-releasing peptide (GRP) receptor, neurotensin receptors, and the
     epidermal growth-factor receptor (EGFR).  Signal-transduction mols.
     activated by these neuropeptides include Src, focal adhesion kinase (FAK),
     ERK, and PI3K/Akt, with subsequent activation of Elk-1, NF-κB, and
     c-myc transcription factors.  A multitude of genes are then expressed by
     prostate cancer cells, which are involved in proliferation,
     anti-apoptosis, migration, metastasis, and angiogenesis.  Targeting of
     these pathways at multiple levels can be exploited to inhibit the process
     by which NE cells contribute to the progression of androgen-independent,
     treatment-refractory prostate cancer.
CC   14 (Mammalian Pathological Biochemistry)
IT   INDEXING IN PROGRESS
IT   Angiogenesis
     Cell migration
       Prostate gland, neoplasm
```

(targeting genes involved in proliferation, anti-apoptosis, migration, metastasis, angiogenesis could be used to inhibit process by which NE cells contribute to progression of **androgen-independent**, treatment-refractory prostate cancer)

REFERENCE COUNT: 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:48929 HCAPLUS
DOCUMENT NUMBER: 142:168784
TITLE: Androgen-independent prostate cancer: target evolution and disease dynamics
AUTHOR(S): Ryan, Charles J.; Small, Eric J.
CORPORATE SOURCE: Urologic Oncology Program, Department of Medicine, UCSF Comprehensive Cancer Center, University of California, San Francisco, CA, 94143, USA
SOURCE: Drug Discovery Today: Disease Mechanisms (2004), 1(2), 223-228
CODEN: DDTDAO; ISSN: 1740-6765
URL: http://www.sciencedirect.com/science/journal/1740 6765
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; **General Review**; (online computer file)
LANGUAGE: English
AB A review with refs. Prostate cancer is a biol. diverse disease. The hallmark of the disease is its ability to regress, and ultimately regrow, following testosterone deprivation (hormone therapy). Recent developments have yielded new insights into the biol. mechanisms of androgen independent growth. In turn, novel therapies directed at these mechanisms, including adrenal androgens, the insulin-like growth factors and transforming growth factor-beta, are being pursued in clin. trials.
CC 1-0 (Pharmacology)
Section cross-reference(s): 2, 14
IT Antitumor agents
Drug targets
Human
Prostate gland, neoplasm
(**androgen-independent** prostate cancer dynamics and therapeutic target evolution)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1072615 HCAPLUS
TITLE: Prostate epithelial cell differentiation and its relevance to the understanding of prostate cancer therapies
AUTHOR(S): Long, Ronan M.; Morrissey, Colm; Fitzpatrick, John M.; Watson, R. William G.
CORPORATE SOURCE: Department of Surgery, Mater Misericordiae University Hospital and Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ire.
SOURCE: Clinical Science (2005), 108(1), 1-11
CODEN: CSCIAE; ISSN: 0143-5221
PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB Prostate cancer is the most common malignancy in males in the western world. However, little is known about its origin and development. This review highlights the biol. of the normal prostate gland and the differentiation of basal epithelial cells to a secretory phenotype. Alterations in this differentiation process leading to cancer and androgen-independent disease are discussed, as well as a full characterization of prostate epithelial cells. A full understanding of the origin and characteristics of prostate cancer epithelial cells will be important if we are to develop therapeutic strategies to combat the heterogeneous nature of this disease.
CC 14 (Mammalian Pathological Biochemistry)
IT INDEXING IN PROGRESS
IT Androgens
Human
Prostate gland
Prostate gland, neoplasm
(prostate epithelial cell differentiation to secretory phenotypes and its relevance will be important to develop therapeutic strategies to combat **androgen-independent** prostate cancer in human)
REFERENCE COUNT: 147 THERE ARE 147 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:818275 HCAPLUS
DOCUMENT NUMBER: 142:86741
TITLE: Ligand-dependent and independent activation of the androgen receptor and implications for therapy
AUTHOR(S): Klocker, Helmut; Culig, Zoran; Eder, Iris; Nessler-Manardi, Claudia; Iotova, Iveta; Hobisch, Alfred; Bartsch, Georg
CORPORATE SOURCE: Department of Urology, University of Innsbruck, Innsbruck, A--6020, Austria
SOURCE: Prostate (2004), 71-82. Editor(s): Habib, Fouad K. Taylor & Francis Ltd.: London, UK. CODEN: 69FWUC; ISBN: 1-84184-140-4
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English
AB A review. Androgen receptor (AR) is expressed in all prostate tumor stages and can be activated ligand-dependently by androgens as well as ligand-independently by other hormones and various growth factors. Moreover, the interaction of the AR with other proteins of the intracellular signal transduction cascade may promote prostate tumor growth. Specific topics discussed in this review were: the androgen receptor; LNCaP tumor progression model; alteration of androgen receptor activation in prostate cancer; androgen receptor mutations; androgen receptor overexpression; ligand-independent androgen receptor activation; androgen receptor coactivators; the hyperreactive androgen receptor prostate cancer model; and elimination of androgen receptor protein as an alternative to inhibition of androgen receptor function.
CC 2-0 (Mammalian Hormones)
Section cross-reference(s): 14
IT Human
Prostate gland, neoplasm
Signal transduction, biological

(ligand-dependent and **independent** activation of **androgen** receptor and implications for therapy)
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:713995 HCAPLUS
DOCUMENT NUMBER: 141:258253
TITLE: Ca2+ homeostasis in apoptotic resistance of prostate cancer cells
AUTHOR(S): Prevarskaya, Natalia; Skryma, Roman; Shuba, Yaroslav
CORPORATE SOURCE: INSERM EPI-9938, USTL, Bat. SN3, Laboratoire de Physiologie Cellulaire, Villeneuve d'Ascq, 59655, Fr.
SOURCE: Biochemical and Biophysical Research Communications (2004), 322(4), 1326-1335
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with refs. Ca2+ is a universal messenger regulating many physiol. functions including such an important one, as the ability of the cell to undergo orderly self-destruction upon completion of its mission, called apoptosis. If this function is compromised unwanted cells may eventually take over the tissue turning it into a cancer. Ca2+ dependency of apoptosis, when its all aspects are learned and understood and key mol. players identified, may provide a good opportunity for controlling tumor growth. In the present mini-review we describe the major mol. determinants of Ca2+ homeostasis in prostate cancer cells and establish their role in the transformation to apoptosis-resistant cell phenotypes typical of advanced androgen-independent prostate cancer. We show that the hallmark of such transformation is the inhibition of apoptosis pathway associated with endoplasmic reticulum Ca2+ store depletion.
CC 14-0 (Mammalian Pathological Biochemistry)
IT **Prostate gland, neoplasm**
(**androgen-independent**; Ca2+ homeostasis in apoptotic resistance of prostate cancer cells)
REFERENCE COUNT: 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:499642 HCAPLUS
DOCUMENT NUMBER: 141:405533
TITLE: Novel therapeutic strategies for androgen-independent prostate cancer: an update
AUTHOR(S): Assikis, Vasily J.; Simons, Jonathan W.
CORPORATE SOURCE: Winship Cancer Institute Prostate Cancer Translational Research Program, Emory University, Atlanta, GA, USA
SOURCE: Seminars in Oncology (2004), 31(2, Suppl. 4), 26-32
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Close to 30,000 men will die from prostate cancer in the United States in 2003. Hormonal ablation, the basis of systemic therapy, will invariably fail to control the progression of metastatic prostate cancer in the long run. For many years the only available therapeutic modalities for patients with metastatic androgen independent prostate cancer have been second-line hormonal maneuvers with estrogens or steroids and

chemotherapy. So far, chemotherapy has been shown to confer adequate palliation but no overall survival benefit in prospective randomized controlled trials, and the only chemotherapy drugs approved by the US Food and Drug Administration are mitoxantrone and estramustine. Novel treatment strategies that aim at specific signaling pathways, apoptosis, differentiation, or specific membranous targets are being developed. Such new therapeutic modalities, along with recent data on immunotherapy and bone targeting strategies, will be reviewed here.

CC 1-0 (Pharmacology)

IT Bone, neoplasm
Prostate gland, neoplasm
(**metastasis**; novel therapeutic strategies along with recent data on immunotherapy, bone targeting strategies for patient with **androgen-independent** prostate cancer are discussed)

REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:350416 HCAPLUS
DOCUMENT NUMBER: 142:52885
TITLE: G protein-coupled receptor (GPCR) and androgen-independent prostate cancer
AUTHOR(S): Bai, Qiang
CORPORATE SOURCE: Renjin Hospital, Shanghai Second Medical University, Shanghai, 200001, Peop. Rep. China
SOURCE: Zhongguo Nankexue Zazhi (2003), 17(4), 280-282
CODEN: ZNZHA4; ISSN: 1008-0848
PUBLISHER: Shanghai Dier Yike Daxue
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Chinese

AB A review, on roles of G protein-coupled receptors (GPCRs) in androgen-independent prostate cancer, discussing mol. characteristics of GPCRs; GPCRs regulation of cell proliferation; GPCRs and androgen receptors in prostate cancers; and mechanism of GPCRs induction of prostate cancer proliferation.

CC 14-0 (Mammalian Pathological Biochemistry)

IT **Prostate gland, neoplasm**
(**androgen-independent**; roles of G protein-coupled receptors in pathogenesis of **androgen-independent** prostate cancer)

L9 ANSWER 8 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:313056 HCAPLUS
DOCUMENT NUMBER: 141:293082
TITLE: Androgen-independent prostate cancer progression: mechanistic insights
AUTHOR(S): Thomas, George V.; Sawyers, Charles L.
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, University of California, Los Angeles, CA, USA
SOURCE: Hormones, Genes, and Cancer (2003), 331-342.
Editor(s): Henderson, Brian E.; Ponder, Bruce; Ross, Ronald K. Oxford University Press, Inc.: New York, N. Y.
CODEN: 69FGQS; ISBN: 0-19-513576-8
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English

AB A review discusses the current mechanistic concepts involved in the development of androgen-independent (AI) prostate cancer. These

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                 ,NT/CT(L)ANDROGEN
L6           352 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "PROSTATE GLAND, NEOPLASM"+PFT
                 ,NT/CT(L)DEPENDENT
L8           138 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 AND L6
L10            8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND REVIEW/DT


=> d l10 ibib abs hitind 1-8

L10  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:818275  HCAPLUS
DOCUMENT NUMBER:          142:86741
TITLE:                    Ligand-dependent and independent activation of the
                          androgen receptor and implications for therapy
AUTHOR(S):                Klocker, Helmut; Culig, Zoran; Eder, Iris;
                          Nessler-Manardi, Claudia; Iotova, Iveta; Hobisch,
                          Alfred; Bartsch, Georg
CORPORATE SOURCE:         Department of Urology, University of Innsbruck,
                          Innsbruck, A-6020, Austria
SOURCE:                   Prostate (2004), 71-82.  Editor(s): Habib, Fouad K.
                          Taylor & Francis Ltd.: London, UK.
                          CODEN: 69FWUC; ISBN: 1-84184-140-4
DOCUMENT TYPE:            Conference; General Review
LANGUAGE:                 English
AB   A review.  Androgen receptor (AR) is expressed in all prostate tumor
     stages and can be activated ligand-dependently by androgens as well as
     ligand-independently by other hormones and various growth factors.
     Moreover, the interaction of the AR with other proteins of the
     intracellular signal transduction cascade may promote prostate tumor
     growth.  Specific topics discussed in this review were: the androgen
     receptor; LNCaP tumor progression model; alteration of androgen receptor
     activation in prostate cancer; androgen receptor mutations; androgen
     receptor overexpression; ligand-independent androgen receptor activation;
     androgen receptor coactivators; the hyperreactive androgen receptor
     prostate cancer model; and elimination of androgen receptor protein as an
     alternative to inhibition of androgen receptor function.
CC   2-0 (Mammalian Hormones)
     Section cross-reference(s): 14
IT   Human
       Prostate gland, neoplasm
     Signal transduction, biological
        (ligand-dependent and independent activation of
        androgen receptor and implications for therapy)
REFERENCE COUNT:          49    THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10  ANSWER 2 OF 8  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2003:277164  HCAPLUS
DOCUMENT NUMBER:          139:4461
TITLE:                    Prostate cancer and androgen receptor in males
AUTHOR(S):                Tanaka, Hiromiki
CORPORATE SOURCE:         Kosei General Hospital, Japan
SOURCE:                   Annual Review Naibunpi, Taisha (2003) 258-262
                          CODEN: ARNTC7
PUBLISHER:                Chugai Igakusha
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DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review on role of androgen receptor in androgen-dependent and independent prostate cancers in males with relapses. The topics discussed are (1) protein motifs and activation of androgen receptor (AR); (2) decreased androgen level and enhanced AR production in prostate cancer with hypersensitive AR; (3) AR and coregulator mutations in prostate cancer with promiscuous AR activity; (4) growth factor upregulation and tyrosine kinase activation and PTEN mutation in AR-dependent androgen-independent prostate cancer; and (5) BCL2 over expression and malignant epithelial stem cells in AR-independent androgen-independent prostate cancer.
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2
IT Human
Prostate gland, neoplasm
(**androgen** receptor in **androgen-dependent** and independent prostate cancers in males)

L10 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:89449 HCAPLUS
DOCUMENT NUMBER: 139:62354
TITLE: Antiandrogens: selective androgen receptor modulators
AUTHOR(S): Berrevoets, Cor A.; Umar, Arzu; Brinkmann, Albert O.
CORPORATE SOURCE: Department of Reproduction and Development, Erasmus University Medical Centre Rotterdam, Rotterdam, DR-3000, Neth.
SOURCE: Molecular and Cellular Endocrinology (2002), 198(1-2), 97-103
CODEN: MCEND6; ISSN: 0303-7207
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Antiandrogens can efficiently block androgen receptor (AR) mediated gene expression, and are therefore useful tools in the treatment of androgen dependent prostate cancer. Antiandrogens are either complete or partial inhibitors of AR activity, depending on the nature of the compound As compared to androgens, antiandrogens induce a different AR conformation, thereby influencing the recruitment of co-regulators (coactivators and corepressors). This ligand-selective modulation of AR activity is affected by an AR mutation (Thr877Ala substitution) found in prostate cancer. In contrast to the wild-type AR, the mutant AR conformation induced by cyproterone acetate (CPA) and hydroxyflutamide (OHF) is comparable to that induced by androgens. As a consequence, this might affect recruitment of co-regulators, thereby allowing CPA and OHF to act as strong agonists on the mutant AR.
CC 1-0 (Pharmacology)
Section cross-reference(s): 2
IT Antitumor agents
Human
Prostate gland, neoplasm
(antiandrogens as selective **androgen** receptor modulators and implivations for treatment of **androgen-dependent** prostate cancer)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:580226 HCAPLUS

DOCUMENT NUMBER: 138:130410
TITLE: Prostate cancer: Status of current treatments and emerging antisense-based therapies
AUTHOR(S): Devi, Gayathri R.
CORPORATE SOURCE: AVI BioPharma Inc, Corvallis, OR, 97333, USA
SOURCE: Current Opinion in Molecular Therapeutics (2002), 4(2), 138-148
CODEN: CUOTFO; ISSN: 1464-8431
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Prostate cancer, like most other solid tumors, represents a heterogeneous entity consisting of a mixture of androgen-dependent and androgen-independent cells. Although proliferation of prostate tumor cells is often initially androgen-dependent, the inevitable development of androgen-insensitivity in late-stage prostate cancer renders androgen-suppressing treatments ultimately ineffective. Non-hormonal chemotherapy induces apoptosis in actively proliferating cells and is typically of little value, since prostate cancer demonstrates very slow growth kinetics. Objective response rates of < 10% and no improved survival rates have been observed in several hundred clin. studies using both exptl. and approved chemotherapeutic agents. An improved understanding of the mol. mechanisms responsible for the onset of the disease, as well as the factors that control the proliferation of prostate cancer cells, have identified key changes in gene expression during cancer progression, especially from androgen-dependent to androgen-independent status. Manipulation of the genes implicated in disease progression represent an important approach for therapeutic intervention. This review summarizes recent progress that has been made with the use of antisense technol. with various chemistries to modify gene expression, a strategy that seems to hold great promise for prostate cancer therapy.

CC 1-0 (Pharmacology)
IT Angiogenesis inhibitors
Antitumor agents
Apoptosis
Human
Prostate gland, neoplasm
(**androgen-dependent** and independent prostate cancer: status of current treatments and emerging antisense-based therapies)
REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:222132 HCAPLUS
DOCUMENT NUMBER: 137:211397
TITLE: Structure and function of GC79/TRPS1, a novel androgen-repressible apoptosis gene
AUTHOR(S): Chang, G. T. G.; van den Bemd, G.-J. C. M.; Jhamai, M.; Brinkmann, A. O.
CORPORATE SOURCE: Department of Endocrinology & Reproduction, Erasmus University Medical Center Rotterdam, Rotterdam, 3000 DR, Neth.
SOURCE: Apoptosis (2002), 7(1), 13-21
CODEN: APOPFN; ISSN: 1360-8185
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with refs. Expression of death-signaling genes induces many biochem. cascades resulting in elimination of cells via apoptosis or programmed cell death. GC79/TRPS1 is a novel apoptosis associated gene that encodes a multitype zinc finger GATA-type transcription factor. Expression of GC79/TRPS1 is repressed in the rat ventral prostate and significantly elevated after androgen withdrawal by castration. Castration leads to regression of the prostate caused by apoptosis of androgen-dependent prostate cells. Prostate cancer consists of androgen-dependent and androgen-independent cells. The androgen-independent cells, usually present in the prostate of advanced prostate cancer patients do not have the ability to undergo apoptosis after androgen withdrawal. GC79/TRPS1 expression in androgen-dependent prostate cancer cells is repressed by androgens, while GC79/TRPS1 expression is hardly detectable in androgen-independent prostate cancer cells under cell culture conditions. This suggests that lack of GC79/TRPS1 expression could be a mechanism for the inability to induce the apoptotic pathway in androgen-independent prostate cancer cells after androgen withdrawal. This review will focus on the current knowledge of the structure and function of GC79/TRPS1, a novel androgen-repressible apoptosis gene.

CC 3-0 (Biochemical Genetics)
Section cross-reference(s): 13

IT **Prostate gland, neoplasm**
(**androgen-dependent**, GC79/TRPS1 expression in, repressed by **androgens**; structure and function of GC79/TRPS1, novel **androgen**-repressible apoptosis gene)

REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:396338 HCAPLUS
DOCUMENT NUMBER: 135:102619
TITLE: Ligand dependent and independent activation of the androgen receptor
AUTHOR(S): Mora, Gloria R.; Tindall, Donald J.
CORPORATE SOURCE: Dep. Biochem. Mol. Biol., Mayo Foundation, Rochester, MN, USA
SOURCE: Prostate Cancer (2001), 219-239. Editor(s): Chung, Leland W. K.; Isaacs, William B.; Simons, Jonathan W. Humana Press Inc.: Totowa, N. J.
CODEN: 69BIZN
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English

AB A review with 148 refs. Androgens play a pivotal role in the embryonic development, growth, and function of many tissues within male species. The cells of these tissues are influenced by androgens through the binding and resultant conformational changes in the androgen receptor (AR). The importance of the role played by ARs in the life of androgen dependent tissues is evidenced in the genetic diseases that produce alterations in the AR, resulting in alterations in the male phenotype. Most of the available knowledge regarding the function of androgens and the role of AR has been obtained from studies of the prostate gland. These studies have elucidated the importance of androgens in the maintenance of homeostasis. The prostate provides a physiol. tissue model of AR action. The study of prostate cancer also provides a pathophysiol. model for the investigation of androgens and AR. Androgen ablation therapies in prostate cancer take advantage of the continued requirement of the androgen-AR relationship in the immortalized tumor cells. Unfortunately, these therapies often fail

with time, and the disease progresses to an androgen refractory and/or androgen independent stage. Recent studies have begun to pull back the veil regarding the pathophysiol. of these refractory cells and the role of AR in their growth. The literature addressing the theme of this chapter is extensive. An exhaustive review of the topic is unnecessary in this context, and interested readers should refer to the more extensive reviews available from the authors' laboratory and others. The goal of this paper is to provide a highlighted review of the current knowledge regarding the function of AR in the presence and absence of ligand. This paper also addresses some of the unanswered questions regarding the role for AR in prostate cancer beyond its classical ligand dependent action.

CC 2-0 (Mammalian Hormones)

IT **Prostate gland**
(**neoplasm**; ligand **dependent** and independent activation of **androgen** receptor)

REFERENCE COUNT: 152 THERE ARE 152 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:842649 HCAPLUS

DOCUMENT NUMBER: 134:347846

TITLE: Emerging drugs for the third millennium. Discovery and development of the inhibitors of steroid 5α-reductase as drugs for the androgen-dependent diseases

AUTHOR(S): Guarna, Antonio; Occhiato, Ernesto G.; Machetti, Fabrizio; Danza, Giovanna; Serio, Mario

CORPORATE SOURCE: Dipartimento di Chimica Organica "Ugo Schiff" e Centro C.N.R sulla Chimica e la Struttura dei Composti Eterociclici, Universita di Firenze, Florence, I-50121, Italy

SOURCE: Seminars in Organic Synthesis, Summer School "A. Corbella", 25th, Gargnano, Italy, June 12-16, 2000 (2000), 41-68. Societa Chimica Italiana: Rome, Italy. CODEN: 69AQRY

DOCUMENT TYPE: Conference; **General Review**

LANGUAGE: English

AB A review with 39 refs. The inhibitors of steroids-5α-reductase (5αR) represent a new class of compds. having all the potentiality for application as drugs in the treatment of a large number of very important and human endocrine-dependent diseases. One of these compds., Finasteride, is already marketed for benign prostatic hyperplasia (BPH) treatment. Other compds. such as Dutasteride are in final clin. phase for application to BPH and alopecia. A new class of 5αR-1 selective inhibitors seems very promising for the treatment of polycystic ovarian syndrome and hirsutism, and for prostatic cancer. On the other hand, the discovery of aza-analogs of steroids and of non-steroidal compds. which can be considered steroid-mimetics, has a strong analogy with the recent development of the peptidomimetic synthesis and the aza-sugar chemical

CC 1-0 (Pharmacology)
Section cross-reference(s): 2

IT **Prostate gland**
(**neoplasm**, inhibitors; inhibitors of steroid 5α-reductase as drugs for the **androgen-dependent** diseases)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:725466 HCAPLUS
DOCUMENT NUMBER: 123:140416
TITLE: Growth of the androgen-dependent tumor of the prostate: role of androgens and of locally expressed growth modulatory factors
AUTHOR(S): Limonta, Patrizia; Dondi, Donatella; Montagnani Marelli, Marina; Moretti, Roberta M.; Negri-Cesi, Paola; Motta, Marcella
CORPORATE SOURCE: Center for Endocrinological Oncology, University of Milano, Milan, 20133, Italy
SOURCE: Journal of Steroid Biochemistry and Molecular Biology (1995), 53(1-6), 401-5
CODEN: JSBBEZ; ISSN: 0960-0760
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with 43 refs., on expts. performed to clarify: (1) the metabolism of androgens in prostatic tumor cells; and (2) the role played by locally produced growth factors in the autocrine regulation of prostatic tumor cell proliferation and the possible regulation exerted by testosterone (T) on the activity of these factors. These studies have been performed by utilizing the human androgen-responsive prostatic cancer LNCaP cell line. By incubating LNCaP cells with different 14C-labeled androgenic precursors, it has been shown that all the major key enzymes involved in the metabolism of androgens are present and active in these cells. In particular, the 5α-reductase, which converts T and androst-4-en-3,17-dione (Δ4) to 17β-hydroxy-5α-androstan-3-one (DHT) and 5α-androstan-3,17-dione (5α-A) resp., seems to be more active when Δ4 is the substrate, suggesting a preference for this precursor. The hypothesis that LNCaP cells might produce LHRH (or a LHRH-like peptide) has been verified by RT-PCR, performed in the presence of a pair of specific oligonucleotide primers. A cDNA band of the expected size (228 bp), which specifically hybridized with a 32P-labeled LHRH oligonucleotide probe, has been obtained in LNCaP cells. To clarify the possible role played by this factor in the regulation of tumor growth, LNCaP cells, cultured in steroid-free conditions, have been treated with a LHRH antagonist; the treatment resulted in a significant increase of cell proliferation. Taken together, these data indicate that LHRH (or LHRH-like) growth modulatory system is expressed in LNCaP cells and plays an inhibitory role in the regulation of tumor cell proliferation. This system seems to be regulated in a neg. way by steroids. Growth factors endowed with stimulatory activity, such as EGF and TGFα, have also been shown to be produced by LNCaP cells. The present studies show that the immunopptn. of the EGF receptor with a specific monoclonal antibody (Ab225) reveals a protein band of the expected size (170 kDa) which is phosphorylated even in basal conditions. Moreover, the treatment of LNCaP cells, cultured in serum-free conditions, either with a monoclonal antibody against the EGF receptor, or with immunoneutralizing antibodies against EGF and TGFα, results in a significant decrease of cell proliferation. These observations clearly confirm the expression, in prostatic tumor cells, of an EGF/TGFα loop which exerts a stimulatory action on cell proliferation. T seems to exert a pos. regulation on this loop, at least in terms of EGF receptor concentration

CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2

IT **Prostate gland**
(**neoplasm**, **carcinoma**, growth of **androgen-dependent** prostate tumor in response to **androgens** and locally expressed growth modulatory factors)

mechanisms can be broadly categorized as those known to signal through the androgen receptor and those whose mechanism for promoting AI growth remains unclear.

CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2

IT Human
Prostate gland, neoplasm
Signal transduction, biological
(**androgen-independent** prostate cancer progression)

REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:115868 HCAPLUS
DOCUMENT NUMBER: 140:297628
TITLE: New features in the treatment of androgen-independent prostate cancer
AUTHOR(S): Closset, Jean; Ammar, Hayet; Nguyen, Viet-Ha; Cornet, Anne; Reiter, Eric
CORPORATE SOURCE: Biochimie, Lab. d'Endocrinologie, Institut Pathologie B23, Universite de Liege, Liege, 4000, Belg.
SOURCE: Current Pharmaceutical Design (2004), 10(5), 513-522
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Prostate cancer develops from clones that are already present as early as thirty-five years of age, when circulating concns. of androgens are high. The progression of the disease is low and the cancer is diagnosed at a more advanced age. Prostate cancer evolves from an androgen dependant stage to stage where it escapes from all anti-androgenic treatments. The patient usually dies within two years following the diagnosis of advanced cancer. Therefore, it is of great interest to develop new therapies for androgen independent prostate cancer. The androgen independent evolution of prostate cancer is a complex phenomenon at the cellular and mol. levels. It includes an increased sensitivity to growth factors, the control of proliferation pathways, apoptotic and survival pathways as well as the control of angiogenesis. Epidemiol. studies have also suggested that certain vitamins or phyto-estrogens could protect against prostate cancer development. The present review attempts to present an overview of the fundamental research in cellular signaling which could be interesting as target for the treatment of androgen independent prostate cancer. Also the potential interest of non-androgenic steroids was reviewed for the same goal.

CC 2-0 (Mammalian Hormones)
Section cross-reference(s): 14

IT Antitumor agents
Prostate gland, neoplasm
Signal transduction, biological
(new features treatment of **androgen-independent** prostate cancer)

REFERENCE COUNT: 126 THERE ARE 126 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:970265 HCAPLUS

DOCUMENT NUMBER: 140:91547
TITLE: Akt in prostate cancer: Possible role in androgen-independence
AUTHOR(S): Ghosh, Paramita M.; Malik, Shazli; Bedolla, Roble; Kreisberg, Jeffrey I.
CORPORATE SOURCE: Department of Surgery, Audie L. Murphy Veterans Administration Hospital, University of Texas Health Science Center at San Antonio and South Texas Veterans Health Care System, San Antonio, TX, USA
SOURCE: Current Drug Metabolism (2003), 4(6), 487-496
CODEN: CDMUBU; ISSN: 1389-2002
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Akt, a downstream effector of phosphatidylinositol 3-kinase (PI3K), has often been implicated in prostate cancer. Studies in prostate tumor cell lines revealed that Akt activation is probably important for the progression of prostate cancer to an androgen-independent state. Investigations of human prostate cancer tissues show that although there is neither Akt gene amplification nor enhanced protein expression in prostate cancer compared to normal tissue, poorly differentiated tumors exhibit increased expression of a phosphorylated (activated) form of Akt compared to normal tissue, prostatic intraepithelial neoplasia (PIN) or well-differentiated prostate cancer. Akt phosphorylation is accompanied by the inactivation of ERK, a member of the mitogen activated protein kinase (MAPK) family. In this article, we postulate that Akt promotes androgen-independent survival of prostate tumor cells by modulating the expression and activation of the androgen receptor (AR).
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2
IT **Prostate gland, neoplasm**
(**carcinoma**; Akt promoted **androgen-independent** survival of prostate tumor by modulating expression and activation of **androgen** receptor)
REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:789145 HCAPLUS
DOCUMENT NUMBER: 140:228081
TITLE: The Evolving Role of Docetaxel in the Management of Androgen Independent Prostate Cancer
AUTHOR(S): Khan, Masood A.; Carducci, Michael A.; Partin, Alan W.
CORPORATE SOURCE: James Buchanan Brady Urological Institute, Johns Hopkins Medical Institution, Baltimore, MD, USA
SOURCE: Journal of Urology (Hagerstown, MD, United States) (2003), 170(5), 1709-1716
CODEN: JOURAA; ISSN: 0022-5347
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Androgen independent prostate cancer is an advanced disease with an extremely poor outcome. In view of this fact, a great deal of interest has recently been generated in the potential use of chemotherapeutic agents, particularly docetaxel. We reviewed the evolving role of docetaxel as a chemotherapeutic agent for the management of this disease. The main emphasis of this review is discussion of the various

clin. trials that have investigated the use of docetaxel alone or combined with other agents for androgen independent prostate cancer. Docetaxel, which acts primarily by inhibiting microtubular depolymn., in combination with other agents has consistently demonstrated a palliative response, a decrease in serum prostate specific antigen levels by 50% or greater in more than 60% of patients, a decrease in measurable disease and the suggestion of improved survival. Docetaxel based regimens are moderately well tolerated and they have shown promising results in various phase 2 trials. The completion of ongoing phase III randomized trials are eagerly awaited since they may determine whether a definite beneficial impact on overall survival can be achieved.

CC 1-0 (Pharmacology)

IT Antitumor agents
Human
Prostate gland, neoplasm
(evolving role of Docetaxel in management of **androgen independent** prostate cancer)

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:496303 HCAPLUS
DOCUMENT NUMBER: 139:147343
TITLE: Signal transduction targets in androgen-independent prostate cancer
AUTHOR(S): Zhou, Jian; Scholes, Jessica; Hsieh, Jer-Tsong
CORPORATE SOURCE: Department of Urology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA
SOURCE: Developments in Oncology (2002), 81(Prostate Cancer: New Horizons in Research and Treatment), 215-226
CODEN: DEOND5; ISSN: 0167-4927
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Prostate cancer (PCa) first manifests as an androgen-dependent disease. Thus, androgen-deprivation therapy is a standard regimen for patients with metastatic PCa. Despite the initial success of androgen-deprivation therapy, PCa inevitably progresses from being androgen dependent (AD) to androgen independent (AI), and this marks the poor prognosis of this disease. Relapse of AIPCa becomes life threatening and accounts for the majority of mortality of PCa patients. Currently, no effective therapy is available for controlling AIPCa. Therefore, the challenge in providing a new intervention is to understand the fundamental changes that occur in AIPCa. Increasing evidence indicates that, under androgen-deprived milieu, several signal networks elicited by peptide growth factors dictate the AI phenotype of PCa. This review covers the latest studies investigating the potential involvement of autocrine growth factors in cell proliferation, survival, metastasis, and the reciprocal interaction with the androgen receptor pathway. In addition, loss of the neg. feedback mechanism of the signal cascade further amplifies the effect of growth factors, and thus contributes significantly to the onset of AIPCa. The understanding of the signal target(s) in AIPCa should provide the new markers for prognosis and a new strategy for prevention and therapy.

CC 14-0 (Mammalian Pathological Biochemistry)

IT **Prostate gland, neoplasm**
(**androgen-independent**; signal transduction targets in **androgen-independent** prostate cancer)

REFERENCE COUNT: 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:328748 HCAPLUS
DOCUMENT NUMBER: 139:50711
TITLE: Androgen-independent prostate cancer: potential role of androgen and ErbB receptor signal transduction crosstalk
AUTHOR(S): El Sheikh, Soha Salama; Domin, Jan; Abel, Paul; Stamp, Gordon; Lalani, El-Nasir
CORPORATE SOURCE: Department of Histopathology, Imperial College, London, UK
SOURCE: Neoplasia (New York, NY, United States) (2003), 5(2), 99-109
CODEN: NEOPFL; ISSN: 1522-8002
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. In prostate cancer (PC), increasing evidence suggests that androgen receptor (AR) signaling is functional under conditions of maximal androgen blockade. PC cells survive and proliferate in the altered hormonal environment possibly by interactions between growth factor-activated pathways and AR signaling. The present review article summarizes the current evidence of this crosstalk and focuses on the interactions among the ErbB receptor network, its downstream pathways, and the AR. The potential role of this crosstalk in the development of androgen independence and in relation to antiandrogen therapy is discussed. Such interactions provide insight into possible complementary or addnl. strategies in the management of PC.
CC 14-0 (Mammalian Pathological Biochemistry)
IT **Prostate gland, neoplasm**
Signal transduction, biological
(**androgen** and ErbB receptor signaling in **androgen-independent** prostate cancer)
REFERENCE COUNT: 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:277164 HCAPLUS
DOCUMENT NUMBER: 139:4461
TITLE: Prostate cancer and androgen receptor in males
AUTHOR(S): Tanaka, Hiromiki
CORPORATE SOURCE: Kosei General Hospital, Japan
SOURCE: Annual Review Naibunpi, Taisha (2003) 258-262
CODEN: ARNTC7
PUBLISHER: Chugai Igakusha
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review on role of androgen receptor in androgen-dependent and independent prostate cancers in males with relapses. The topics discussed are (1) protein motifs and activation of androgen receptor (AR); (2) decreased androgen level and enhanced AR production in prostate cancer with hypersensitive AR; (3) AR and coregulator mutations in prostate cancer with promiscuous AR activity; (4) growth factor upregulation and tyrosine kinase activation and PTEN mutation in AR-dependent androgen-independent

prostate cancer; and (5) BCL2 over expression and malignant epithelial stem cells in AR-independent androgen-independent prostate cancer.
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2
IT Human
Prostate gland, neoplasm
(**androgen** receptor in **androgen**-dependent and **independent** prostate cancers in males)

L9 ANSWER 15 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:780480 HCAPLUS
DOCUMENT NUMBER: 137:288382
TITLE: Novel clinical trials in androgen-independent prostate cancer
AUTHOR(S): Gulley, James; Dahut, William
CORPORATE SOURCE: National Cancer Institute, Bethesda, MD, USA
SOURCE: Clinical Prostate Cancer (2002), 1(1), 51-57
CODEN: CPCLC4; ISSN: 1540-0352
PUBLISHER: Cancer Information Group
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Current treatments for androgen-independent prostate cancer have not shown a definitive increase in survival. Several novel drugs have made their way through preclin. testing into early clin. trials. Targets discussed in this review include apoptosis, antiangiogenesis, growth factor receptors or associated tyrosine kinases, and tumor-associated antigens targeted by vaccines. Research in this area includes testing combinations of previously studied chemotherapeutic agents as well as identifying and testing novel agents. It is these drugs, either alone or in combination, that are designed to target strategic pathways to improve survival and increase quality of life in prostate cancer patients. This review focuses on the novel agents being tested with chemotherapy in metastatic prostate cancer.
CC 1-0 (Pharmacology)
IT **Prostate gland, neoplasm**
(**metastasis**; novel clin. trials in **androgen-independent** prostate cancer and prostate cancer metastasis patients)
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 16 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:780475 HCAPLUS
DOCUMENT NUMBER: 138:313663
TITLE: Antisense therapy: recent advances and relevance to prostate cancer
AUTHOR(S): Benimetskaya, Luba; Stein, C. A.
CORPORATE SOURCE: Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, USA
SOURCE: Clinical Prostate Cancer (2002), 1(1), 20-30
CODEN: CPCLC4; ISSN: 1540-0352
PUBLISHER: Cancer Information Group
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Currently employed treatment options for patients with advanced and metastatic cancer such as surgery, radiation, hormone therapy, and chemotherapy are limited. In particular, the well known limitations of chemotherapy are at least in part due to a lack of specificity. The

activation of dominant oncogenes and inactivation of tumor suppressor genes may represent novel targets for cancer therapy. Antisense therapy has been widely used to specifically and selectively inhibit the expression of selected genes at the mRNA level. Combinations of antisense oligonucleotides with chemotherapeutic agents may offer important advantages in cancer treatment. Several antisense drugs, especially oblimersen (G3139), have shown interesting results in expts. in animals, and have entered clin. trials. However, control oligonucleotides must be carefully chosen to sep. antisense effects from the many potential nonspecific effects of oligonucleotides. This review summarizes the advantages and limitations of antisense therapy and its use in the treatment of androgen-independent prostate cancer.

CC 1-0 (Pharmacology)

IT Antitumor agents
Human
Prostate gland, neoplasm
(antisense therapy of **androgen-independent** prostate cancer)

REFERENCE COUNT: 155 THERE ARE 155 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 17 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:580226 HCAPLUS
DOCUMENT NUMBER: 138:130410
TITLE: Prostate cancer: Status of current treatments and emerging antisense-based therapies
AUTHOR(S): Devi, Gayathri R.
CORPORATE SOURCE: AVI BioPharma Inc, Corvallis, OR, 97333, USA
SOURCE: Current Opinion in Molecular Therapeutics (2002), 4(2), 138-148
CODEN: CUOTFO; ISSN: 1464-8431
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Prostate cancer, like most other solid tumors, represents a heterogeneous entity consisting of a mixture of androgen-dependent and androgen-independent cells. Although proliferation of prostate tumor cells is often initially androgen-dependent, the inevitable development of androgen-insensitivity in late-stage prostate cancer renders androgen-suppressing treatments ultimately ineffective. Non-hormonal chemotherapy induces apoptosis in actively proliferating cells and is typically of little value, since prostate cancer demonstrates very slow growth kinetics. Objective response rates of < 10% and no improved survival rates have been observed in several hundred clin. studies using both exptl. and approved chemotherapeutic agents. An improved understanding of the mol. mechanisms responsible for the onset of the disease, as well as the factors that control the proliferation of prostate cancer cells, have identified key changes in gene expression during cancer progression, especially from androgen-dependent to androgen-independent status. Manipulation of the genes implicated in disease progression represent an important approach for therapeutic intervention. This review summarizes recent progress that has been made with the use of antisense technol. with various chemistries to modify gene expression, a strategy that seems to hold great promise for prostate cancer therapy.

CC 1-0 (Pharmacology)

IT Angiogenesis inhibitors
Antitumor agents

Apoptosis
Human
Prostate gland, neoplasm
(**androgen**-dependent and **independent** prostate cancer: status of current treatments and emerging antisense-based therapies)
REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 18 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:481915 HCAPLUS
DOCUMENT NUMBER: 137:308053
TITLE: Signal Transduction Targets in Androgen-independent Prostate Cancer
AUTHOR(S): Zhou, Jian; Scholes, Jessica; Hsieh, Jer-Tsong
CORPORATE SOURCE: Department of Urology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA
SOURCE: Cancer and Metastasis Reviews (2002), Volume Date 2001, 20(3/4), 351-362
CODEN: CMRED4; ISSN: 0167-7659
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Prostate cancer (PCa) first manifests as an androgen-dependent disease. Thus, androgen-deprivation therapy is a standard regimen for patients with metastatic PCa. Despite the initial success of androgen-deprivation therapy, PCa inevitably progresses from being androgen dependent (AD) to androgen independent (AI), and this marks the poor prognosis of this disease. Relapse of AIPCa becomes life threatening and accounts for the majority of mortality of PCa patients. Currently, no effective therapy is available for controlling AIPCa. Therefore, the challenge in providing a new intervention is to understand the fundamental changes that occur in AIPCa. Increasing evidence indicates that, under androgen-deprived milieu, several signal networks elicited by peptide growth factors dictate the AI phenotype of PCa. This review covers the latest studies investigating the potential involvement of autocrine growth factors in cell proliferation, survival, metastasis, and the reciprocal interaction with the androgen receptor pathway. In addition, loss of the neg. feedback mechanism of the signal cascade further amplifies the effect of growth factors, and thus contributes significantly to the onset of AIPCa. The understanding of the signal target(s) in AIPCa should provide the new markers for prognosis and a new strategy for prevention and therapy.
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 1, 2
IT Antitumor agents
Prostate gland, neoplasm
Signal transduction, biological
(signal transduction targets in **androgen-independent** prostate cancer)
REFERENCE COUNT: 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 19 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:344671 HCAPLUS
DOCUMENT NUMBER: 137:214328
TITLE: Mechanisms involved in the progression of

androgen-independent prostate cancers: It is not only the cancer cell's fault
AUTHOR(S): Arnold, J. T.; Isaacs, J. T.
CORPORATE SOURCE: Johns Hopkins Oncology, Bunting Blaustein Cancer Research Building, Baltimore, MD, 21231, USA
SOURCE: Endocrine-Related Cancer (2002), 9(1), 61-73
CODEN: ERCAE9; ISSN: 1351-0088
PUBLISHER: Society for Endocrinology
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. The acquisition of an androgen-independent phenotype by prostate cancer cells is presently a death sentence for patients. In order to have a realistic chance of changing this outcome, an understanding of what drives the progression to androgen independence is critical The authors review here a working hypothesis based on the position that the development of androgen-independent epithelial cells is the result of a series of cellular and mol. events within the whole tissue that culminates in the loss of normal tissue-maintained growth control. This tissue includes the epithelial and stromal cells, the supporting extracellular matrix and circulating hormones. This review discusses the characteristics of these malignant cells, the role of stromal cells involved in growth and the differentiation of epithelial cells, and the role of the extracellular matrix as a mediator of the phenotypes of stromal and epithelial cells. In addition, environmental, neuroendocrine and immune factors that may contribute to disturbance of the fine balance of the epithelial-stromal-extracellular matrix connection are considered. While the goal of many therapeutic approaches to prostate cancer has been androgen ablation or targeting the androgen receptor (AR) of epithelial cells, these therapies become ineffective as the cells progress beyond dependence on androgen for growth control. Twenty years ago Sir David Smithers debated that cancer is the result of loss of tolerance within tissues and the organizational failure of normal growth-control mechanisms. This is precipitated by prolonged or abnormal demands for regeneration or repair, rather than of any inherent disorder peculiar to each of the individual components involved. He wrote 'It is not the cell itself that is disorderly, but its relation with the rest of the tissue'. We have gained significantly large amts. of precise data on the effects of androgenic ablation on cancerous prostate cells and on the role of the AR in prostate cancer. The need has come to compile this information towards a perspective of dysregulation of tissue as a whole, and to develop exptl. systems to address this broader perspective to find and develop therapies for treatment and prevention.

CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2

IT Human
Phenotypes
Prostate gland, neoplasm
(mechanisms involved in progression of **androgen-independent** prostate cancers)

REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 20 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:201850 HCAPLUS
DOCUMENT NUMBER: 137:210190
TITLE: Emerging targets in the AKT pathway for treatment of androgen-independent prostatic adenocarcinoma
AUTHOR(S): Graff, Jeremy R.

CORPORATE SOURCE: Cancer Division, Lilly Research Labs, Lilly Corporate Centre, DC 0546, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Expert Opinion on Therapeutic Targets (2002), 6(1), 103-113
CODEN: EOTTAO; ISSN: 1472-8222
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Prostatic adenocarcinoma (CaP) is the most common, non-cutaneous malignancy and the second-leading cause of cancer death in men. The disease has two distinct phases: the androgen-dependent phase, which can be treated effectively with androgen ablation therapies, and the androgen-independent phase, for which there is no effective life-prolonging therapy. An estimated 32,000 men will die this year from androgen-independent, metastatic CaP. Efforts to understand the metastatic progression of CaP and the emergence of androgen-independent disease have begun to illuminate the mol. events involved. Recent work suggests that CaP progression to androgen-independent, metastatic disease involves a dampened apoptotic response, a release from the cell cycle block that initially follows androgen withdrawal and a shift from dependence on paracrine-derived growth and survival factors to autonomous production of these key proteins. Functional loss of the tumor suppressor phosphatase and tensin homolog deleted on chromosome ten (PTEN) and subsequent activation of the AKT pathway, have been prominently implicated in the progression of CaP to androgen-independence. Activation of the AKT pathway can suppress the apoptotic response, undermine cell cycle control and selectively enhance the production of key growth and survival factors. Though many proteins and intracellular signaling pathways can influence these biol. processes, activation of the AKT pathway may be a particularly potent signal involved in CaP progression to androgen-independence and therefore presents a series of potential targets for therapy of advanced androgen-independent CaP.

CC 1-0 (Pharmacology)

IT **Prostate gland, neoplasm**
(**adenocarcinoma**; emerging targets in AKT pathway for treatment of **androgen-independent** prostatic **adenocarcinoma**)

REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 21 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:605485 HCAPLUS
DOCUMENT NUMBER: 136:303338
TITLE: Novel therapeutic strategy for advanced prostate cancer using antisense oligodeoxynucleotides targeting anti-apoptotic genes upregulated after androgen withdrawal to delay androgen-independent progression and enhance chemosensitivity
AUTHOR(S): Miyake, Hideaki; Hara, Isao; Kamidono, Sadao; Gleave, Martin E.
CORPORATE SOURCE: The Prostate Center, Vancouver General Hospital, Vancouver, BC, Can.
SOURCE: International Journal of Urology (2001), 8(7), 337-349
CODEN: IJURF3; ISSN: 0919-8172
PUBLISHER: Blackwell Science Asia Pty Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Progression to androgen-independence remains the main obstacle to improving survival for patients with advanced prostate cancer. In this review, findings are summarized that have recently been demonstrated to establish novel therapeutic strategy targeting several genes playing functionally important roles after androgen withdrawal and during androgen-independent progression. The authors initially characterized changes in gene expression after androgen withdrawal in the androgen-dependent Shionogi and LNCaP tumor models using cDNA arrays. Based on these results, they focused on genes highly upregulated after androgen ablation (i.e. bcl-2, bcl-xL, TRPM-2, IGFBP-5), which have anti-apoptotic or mitogenic activities, and thereby confer a resistance to androgen withdrawal as well as cytotoxic chemotherapy. The authors further demonstrated the efficacy of an antisense oligodeoxynucleotide (ODN) strategy for patients with advanced prostate cancer through the inhibition of target gene expression, resulting in a delay in the progression to androgen-independence by enhancing apoptotic cell death induced by androgen ablation and chemotherapy. The authors also showed the effectiveness of combined antisense ODN therapy and cytotoxic chemotherapy by achieving additive or synergistic effects. These findings provide a basic significance for the design of clin. studies using antisense ODN either alone or in combination with chemotherapeutic agents in patients with advanced prostate cancer.

CC 1-0 (Pharmacology)

IT **Prostate gland**
(**neoplasm**, inhibitors; prostate cancer treatment using antisense oligodeoxynucleotides targeting anti-apoptotic genes upregulated after **androgen** withdrawal to delay **androgen-independent** progression and enhance chemosensitivity)

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 22 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:396348 HCAPLUS
DOCUMENT NUMBER: 135:102620
TITLE: The role of small bioactive peptides and cell surface peptidases in androgen independent prostate cancer
AUTHOR(S): Nelson, Joel B.
CORPORATE SOURCE: Brady Urol. Inst., Johns Hopkins Med. Inst., Baltimore, MD, USA
SOURCE: Prostate Cancer (2001), 433-447. Editor(s): Chung, Leland W. K.; Isaacs, William B.; Simons, Jonathan W. Humana Press Inc.: Totowa, N. J.
CODEN: 69BIZN
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English

AB A review with 120 refs. At current rates of diagnosis, a man in the United States has a one-in-five chance that invasive prostate cancer will develop in his lifetime. This rate is nearly twice that of lung cancer and three times that of colorectal cancer. Death from prostate cancer is the second leading cause of death from cancer in men in the United States. Almost every man with advanced prostate cancer will undergo androgen ablation therapy and in time, most will progress. The central characteristic of fatal prostate cancer is androgen independence. These facts were established in 1941, when therapeutic castration was first described, and, unfortunately, still hold true as the 1990s drew to a close. Historically, there has been an inverse relationship between efforts to maximize the efficacy of hormonal therapy for prostate cancer

and the outcomes of those efforts: thousands of patients studied and billions of dollars spent repeatedly show hormonal therapy to have dramatic-yet ultimately ineffective-therapeutic effects. Although a number of growth and survival factors have been implicated in the androgen independent phenotype of prostate cancer, there has been no translation of these findings to effective therapy. This review is not confined to the classic neuroendocrine phenotype (which, in its small cell or carcinoid manifestations represents a fraction of prostate cancers)-it examines a recent series of related observations about the role of the small bioactive peptides bombesin, endothelin-1 (ET-1), and neurotensin in prostate cancer. These peptides-which have compelling biol. effects in prostate cancer-act through specific, high-affinity heptahelical, G-protein-coupled receptors. Collectively, recent observations may provide a broader understanding of androgen independent prostate cancer. Excitement for targeting these pathways in therapy has been fueled by early clin. trial results: the use of an endothelin-receptor antagonist has resulted in both objective and subjective responses.

CC 2-0 (Mammalian Hormones)

IT **Prostate gland**
(**neoplasm, androgen-independent**; role of small bioactive peptides and cell surface peptidases in **androgen independent** prostate cancer)

REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 23 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:396338 HCAPLUS
DOCUMENT NUMBER: 135:102619
TITLE: Ligand dependent and independent activation of the androgen receptor
AUTHOR(S): Mora, Gloria R.; Tindall, Donald J.
CORPORATE SOURCE: Dep. Biochem. Mol. Biol., Mayo Foundation, Rochester, MN, USA
SOURCE: Prostate Cancer (2001), 219-239. Editor(s): Chung, Leland W. K.; Isaacs, William B.; Simons, Jonathan W. Humana Press Inc.: Totowa, N. J.
CODEN: 69BIZN
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English

AB A review with 148 refs. Androgens play a pivotal role in the embryonic development, growth, and function of many tissues within male species. The cells of these tissues are influenced by androgens through the binding and resultant conformational changes in the androgen receptor (AR). The importance of the role played by ARs in the life of androgen dependent tissues is evidenced in the genetic diseases that produce alterations in the AR, resulting in alterations in the male phenotype. Most of the available knowledge regarding the function of androgens and the role of AR has been obtained from studies of the prostate gland. These studies have elucidated the importance of androgens in the maintenance of homeostasis. The prostate provides a physiol. tissue model of AR action. The study of prostate cancer also provides a pathophysiol. model for the investigation of androgens and AR. Androgen ablation therapies in prostate cancer take advantage of the continued requirement of the androgen-AR relationship in the immortalized tumor cells. Unfortunately, these therapies often fail with time, and the disease progresses to an androgen refractory and/or androgen independent stage. Recent studies have begun to pull back the veil regarding the pathophysiol. of these refractory cells and the role of

AR in their growth. The literature addressing the theme of this chapter is extensive. An exhaustive review of the topic is unnecessary in this context, and interested readers should refer to the more extensive reviews available from the authors' laboratory and others. The goal of this paper is to provide a highlighted review of the current knowledge regarding the function of AR in the presence and absence of ligand. This paper also addresses some of the unanswered questions regarding the role for AR in prostate cancer beyond its classical ligand dependent action.

CC 2-0 (Mammalian Hormones)

IT **Prostate gland**
(**neoplasm**; ligand dependent and **independent** activation of **androgen** receptor)

REFERENCE COUNT: 152 THERE ARE 152 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 24 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:30811 HCAPLUS
DOCUMENT NUMBER: 135:17532
TITLE: Androgen receptor and its role in the development and control of androgen-independent prostate cancer
AUTHOR(S): Liao, Shutsung; Kokontis, John M.; Hiipakka, Richard A.
CORPORATE SOURCE: The Ben May Institute for Cancer Research, University of Chicago, Chicago, IL, USA
SOURCE: Hormonal Carcinogenesis III, Proceedings of the International Symposium, 3rd, Seattle, WA, United States, Sept. 6-12, 1998 (2001), Meeting Date 1998, 301-306. Editor(s): Li, Jonathan J.; Li, Sara Antonia; Daling, Janet R. Springer-Verlag New York: Secaucus, N. J.
CODEN: 69AURC
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English
AB A review with 12 refs. Topics discussed include the progression of androgen-dependent prostate cancer cells to androgen-independent prostate cancer cells; androgen-dependent induction of cell cycle arrest in androgen-independent prostate cancer cells; androgen receptor-dependent suppression of prostate tumors in mice; the reversion of androgen-independent prostate tumors back to androgen-dependent tumors; and intermittent androgen replacement therapy (IART) and androgen suppression/reversion therapy (ASRT).
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2
IT **Prostate gland**
(**neoplasm**; **androgen** receptors role in development and control of **androgen-independent** prostate cancer)
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 25 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:538306 HCAPLUS
DOCUMENT NUMBER: 134:27966
TITLE: Ligand-independent activation of the androgen receptor in prostate cancer by growth factors and cytokines
AUTHOR(S): Jenster, Guido

CORPORATE SOURCE: Department of Urology, Erasmus University Rotterdam, Rotterdam, 3000 DR, Neth.
SOURCE: Journal of Pathology (2000), 191(3), 227-228
CODEN: JPTLAS; ISSN: 0022-3417
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with 27 refs. During the course of prostate cancer progression, cells convert from an androgen-dependent to an androgen-independent growth status. At this late stage, the role of the androgens testosterone and dihydrotestosterone and their nuclear receptor, the androgen receptor (AR), is unclear. Has the growth pathway, initiated by the AR, been bypassed in androgen-independent tumors. Mounting evidence suggests the opposite. Prostate cancer cells that have acquired the ability to survive and grow in a low-androgen environment might be activating the AR pathway using growth factors, cytokines, and steroids other than androgens.
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2
IT **Prostate gland**
(**neoplasm**; ligand-**independent** activation of the **androgen** receptor in prostate cancer by growth factors and cytokines)
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 26 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:122438 HCAPLUS
DOCUMENT NUMBER: 133:56690
TITLE: Small bioactive peptides and cell surface peptidases in androgen-independent prostate cancer
AUTHOR(S): Nelson, Joel B.; Carducci, Michael A.
CORPORATE SOURCE: Department of Urology, The University of Pittsburgh, Pittsburgh, PA, USA
SOURCE: Cancer Investigation (2000), 18(1), 87-96
CODEN: CINVD7; ISSN: 0735-7907
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with 120 refs., on the titled topic with discussion of the roles of bombesin/gastrin-releasing peptide, endothelin-1, neurotensin, neutral endopeptidase 24.11, and caveolin.
CC 14-0 (Mammalian Pathological Biochemistry)
IT **Prostate gland**
(**neoplasm**; small bioactive peptides and cell surface peptidases in **androgen-independent** prostate cancer)
REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 27 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:620098 HCAPLUS
DOCUMENT NUMBER: 132:135557
TITLE: Markers of androgen-independent progression of prostatic carcinoma
AUTHOR(S): Daliani, Danai; Papandreou, Christos N.
CORPORATE SOURCE: University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Seminars in Oncology (1999), 26(4), 399-406

CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with 112 refs. Prostate cancer (PCa) remains the most common cancer and the second leading cause of cancer mortality in men in the United States. The evolution from a localized to a metastatic phenotype coupled with the progression from an androgen-dependent (AD) to an androgen-independent (AI) state leads to a universally fatal disease. Identifying the biol. characteristics associated with PCa progression is a major goal of current research efforts by different groups, in the hope to better predict the natural history of the disease in an individual patient and to design treatments based on the specific biol. behavior.
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2
IT **Prostate gland**
(**neoplasm, androgen-independent**; **androgen-independent** progression of prostatic **carcinoma** markers)
REFERENCE COUNT: 112 THERE ARE 112 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 28 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:555584 HCAPLUS
DOCUMENT NUMBER: 132:76770
TITLE: Stem cell genes in androgen-independent prostate cancer
AUTHOR(S): Bui, Matthew; Reiter, Robert E.
CORPORATE SOURCE: Department of Urology, Jonsson Comprehensive Cancer Center, UCLA School of Medicine, Los Angeles, CA, USA
SOURCE: Cancer and Metastasis Reviews (1999), Volume Date 1998-1999, 17(4), 391-399
CODEN: CMRED4; ISSN: 0167-7659
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with 60 refs. Despite recent advances in the detection and treatment of early stage prostate cancer, there remains little effective therapy for patients with locally advanced and/or metastatic disease. Although the majority of patients with advanced disease respond initially to androgen ablation therapy, most go on to develop androgen-independent tumors that are inevitably fatal. Therefore, understanding the mechanisms by which a hormone-sensitive tumor escapes hormonal control is critical to the development of effective therapeutic modalities. The study of the differentiation pathways of normal and abnormal prostate growth has led to the development of a stem cell model for prostate cancer [1-3]. Recent work discussed in this commentary suggests that prostate tumors resist apoptosis and proliferate by adopting features of normal prostatic stem/progenitor cells. Basal cells, the putative stem/progenitor cells of the prostate, possess the phenotype of androgen-independence as do most advanced prostate cancers. Therefore, the study of basal cells may prove critical to understanding prostate carcinogenesis and to the development of novel strategies for preventing and managing prostate cancer.
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2
IT **Prostate gland**
(**neoplasm**; stem cell genes in **androgen-**

independent prostate cancer)
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 29 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:581952 HCAPLUS
DOCUMENT NUMBER: 129:342105
TITLE: Apoptosis and other mechanisms in androgen ablation treatment and androgen independent progression of prostate cancer: a review
AUTHOR(S): Westin, Patrick; Bergh, Anders
CORPORATE SOURCE: Department of Pathology, University of Umea, Umea, 901 87, Swed.
SOURCE: Cancer Detection and Prevention (1998), 22(5), 476-484
CODEN: CDPRD4; ISSN: 0361-090X
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 114 refs. Patients with advanced prostate cancer commonly present with disseminated disease. For these patients, androgen ablation is a first-line treatment. This mode of therapy usually has an initially palliative effect on tumor-related symptoms and slows growth, although virtually all tumors eventually relapse to an androgen-independent, more aggressively growing phenotype. However, surprisingly little is known about the actions mediating the initial palliative effect as well as the initiation of androgen-independent tumor growth. In this review, some current concepts on mechanisms of androgen ablation treatment and androgen-independent progression of prostate cancer is highlighted. Special attention is given to the involvement of apoptosis in these processes.
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2
IT **Prostate gland**
(**neoplasm**; apoptosis and other mechanisms in **androgen** ablation treatment and **androgen independent** progression of prostate cancer)
REFERENCE COUNT: 114 THERE ARE 114 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 30 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:544085 HCAPLUS
DOCUMENT NUMBER: 129:254261
TITLE: New approaches to treatment of androgen-independent prostate cancer based on peptide analogs
AUTHOR(S): Schally, A. V.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, VA Medical Center and Section of Experimental Med., Dep. Med., Tulane Univ. Sch. Med., New Orleans, LA, USA
SOURCE: Current Advances in Andrology, Proceedings of the International Congress of Andrology, 6th, Salzburg, May 25-29, 1997 (1997), 81-87. Editor(s): Waites, Geoffrey M. H.; Frick, Julian; Baker, Gordon W. H. Monduzzi Editore: Bologna, Italy.
CODEN: 66MSAS
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English
AB A review with 15 refs. New hormonal methods for treatments of advanced

prostate carcinoma are being developed based on peptide analogs such as antagonists of LH-releasing hormone (LH-RH), analogs of somatostatin, antagonists of growth hormone-releasing hormone (GH-RH) and antagonists of bombesin/gastrin releasing peptide (GRP). These analogs inhibit tumor growth by interfering with the secretion or the receptors of growth factors including epidermal growth factor (EGF), insulin-like growth factor-I (IGF-I) and bombesin/GRP, which may play a role in the progression and the relapse of prostate cancer. A new class of antitumor agents based on LH-RH analogs linked to Doxorubicin and its 2-pyrrolino-derivative, which is 500-1000 times more active, is used for targeted chemotherapy of prostate cancer to produce a local tumoricidal effect. Exptl. results with the analogs in nude mice bearing transplanted human prostate cancer lines and Dunning rat tumor models are summarized as well as clin. findings in patients with advanced prostate cancer. Continued investigation should lead to a more effective therapy for relapsed, androgen-independent prostate cancer.

CC 1-0 (Pharmacology)
Section cross-reference(s): 2

IT **Prostate gland**
(**carcinoma**, **androgen-independent**; new approaches to treatment of **androgen-independent** prostate cancer based on peptide analogs)

IT **Prostate gland**
(**neoplasm**, inhibitors; new approaches to treatment of **androgen-independent** prostate cancer based on peptide analogs)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 31 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:144582 HCAPLUS
DOCUMENT NUMBER: 128:255658
TITLE: Protein kinase, C-α: a novel target for the therapy of androgen-independent prostate cancer? (Review-hypothesis)
AUTHOR(S): O'Brian, Catherine A.
CORPORATE SOURCE: Department of Cell Biology, University of Texas, Houston, TX, 77030, USA
SOURCE: Oncology Reports (1998), 5(2), 305-309
CODEN: OCRPEW; ISSN: 1021-335X
PUBLISHER: Oncology Reports
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with 40 refs. Prostate cancer is a leading cause of cancer death among men in Western countries. A major reason for this is that the malignancy often progresses to an androgen-independent phenotype that is highly aggressive and unresponsive to available therapies. Protein kinase C (PKC) is an isoenzyme family with at least eleven mammalian members that play important roles in cell growth regulation and differentiation. Based on the emerging understanding of the role played by PKC isoenzymes in the regulation of prostate cancer cell growth and programmed death, in this report we develop the hypothesis that a defective PKC-α-mediated apoptotic pathway in androgen-independent human prostate cancer cells has allowed the cells to acquire a selective growth advantage by over-expression of PKC-α and that this adaptive response renders the cells dependent on constitutively active PKC-α for their survival. Studies reviewed in this report provide strong evidence that expression of constitutive PKC-α activity is required for the survival and growth

of androgen-independent human prostate cancer cells, but direct evidence for this is still lacking. We outline exptl. approaches that will be required to definitively test the importance of PKC-α to androgen-independent human prostate cancer cell growth and survival. If constitutive PKC-α activity is in fact found to be required for the growth and survival of androgen-independent human prostate cancer, then the development of PKC-α-targeted therapeutics for use in the clin. treatment of prostate cancer will be justified.

CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 7

IT **Prostate gland**
(**neoplasm**; protein kinase C-α as a novel target for the therapy of **androgen-independent** prostate cancer in human)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 32 OF 32 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:707880 HCAPLUS
DOCUMENT NUMBER: 128:21139
TITLE: Steroid-independent activation of androgen receptor in androgen-independent prostate cancer. A possible role for the MAP kinase signal transduction pathway?
AUTHOR(S): Zhu, X.; Liu, J.-P.
CORPORATE SOURCE: Baker Medical Research Institute, Commercial Road, Prahran Victoria, 3181, Australia
SOURCE: Molecular and Cellular Endocrinology (1997), 134(1), 9-14
CODEN: MCEND6; ISSN: 0303-7207
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 56 refs.
CC 14-0 (Mammalian Pathological Biochemistry)
IT **Prostate gland**
(**neoplasm**; steroid-**independent** activation of **androgen** receptor in **androgen-independent** prostate cancer in relation to the MAP kinase signal transduction pathway)
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT